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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WOITACH, JOSEPH T	
ART UNIT	**PAPER NUMBER**
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/373,938	HALLENBECK ET AL.	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 August 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3,28-31 and 33-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2, 3, 28-31, 33-41, 45-49* is/are rejected.

7)☒ Claim(s) *42-44* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This is an original application filed August 13, 1999.

Applicants amendment filed August 7, 2003 has been received and entered. Claim 1 has been canceled. Claims 2, 28, 33, 38-41, 43-45 and 47-49 have been amended. Claims 2, 3, 28-31 and 33-49 are pending and currently under examination.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 43 and 44 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn.

The amendments to the claims and Applicants' arguments have adequately addressed the basis of the rejections.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 28 and 29 rejected under 35 U.S.C. 102(e) as being anticipated by Crystal *et al.* (US2002/0076395 A1) is withdrawn.

Cancellation of claim 1 and changing the dependency of claims 28 and 29 has differentiated the claimed invention from that disclosed by Crystal *et al.*

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 28, 29, 34-37, 39, 40, 41 rejected under 35 U.S.C. 103(a) as being unpatentable over Folkman *et al.* (WO 96/35774) and O'Reilly *et al.* (US Patent 5,854,205) is withdrawn.

Claims 2 and 3 rejected under 35 U.S.C. 103(a) as being unpatentable over Folkman *et al.* (WO 96/35774) and O'Reilly *et al.* (US Patent 5,854,205) as applied to claims 1, 28, 29, 34-37, 39, 40, 41 in further view of Blezinger *et al.* is withdrawn.

Claim 33 rejected under 35 U.S.C. 103(a) as being unpatentable over Folkman *et al.* (WO 96/35774) and O'Reilly *et al.* (US Patent 5,854,205) as applied to claims 1, 28, 29, 34-37, 40, 41 in further view of Lemarchand *et al.* is withdrawn.

Claims 28-30, 33, 38, 45-49 rejected under 35 U.S.C. 103(a) as being unpatentable over Folkman *et al.* (WO 96/35774) and O'Reilly *et al.* (US Patent 5,854,205) as applied to claims 1, 28, 29, 34-37, 39, 40, 41 in further view of Kovesdi *et al.* is withdrawn.

Claims 28, 29, 31 rejected under 35 U.S.C. 103(a) as being unpatentable over Folkman *et al.* (WO 96/35774) and O'Reilly *et al.* (US Patent 5,854,205) in further view of Kovesdi *et al.* as applied to claims 1, 28-30, 33, 38, 45-49 in further view of Henderson *et al.* (US Patent 6,495,130 B1) is withdrawn.

In each case the specific rejection as previously formulated has been obviated by cancellation of claim 1 and the amendments to the dependent claims. New rejections based on the amended claims are set forth below. Applicants' arguments in traverse of the previous rejections will be discussed to the extent they apply to the new rejections.

Claims 2, 3, 28, 29, 34-37, 39, 40, 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Reilly *et al.* (US Patent 5,854,205), Folkman *et al.* (WO 96/35774), Crystal *et al.* (US2002/0076395 A1) and Blezinger *et al.*

At the time of filing, O'Reilly *et al.* teach anti-angiogenic compositions and methods of use. Specifically, O'Reilly *et al.* teach endostatin sequences derived from the N-terminus of collagen XVIII (see figure 5 and column 2, lines 20-24). O'Reilly *et al.* teach that administration of endostatin to human and animal tumors prevents growth and expansion of the tumor (column 2, lines 31-42). By example, O'Reilly *et al.* teach that administration of both mouse and human endostatins are capable of preventing tumor growth in an animal model (see figure 11). O'Reilly *et al.* demonstrate that various vectors can be used to produce endostatin and the protein produced is effective *in vivo* for reducing tumor size (see for example EXAMPLE 5). Further, O'Reilly *et al.* teach that nucleic acid sequences encoding endostatin can be used in and administered by other methodologies such as gene therapy (column 9, lines 35-37). Similarly, Crystal *et al.* teach methods and materials for treating tissue with anti-angiogenic factors. More specifically, Crystal *et al.* teach that adenoviral vectors are capable and can be used for expressing the anti-angiogenic factor endostatin (see claims 1, 3-8). Demonstrating the ability of an adenoviral vector to express an anti-angiogenic protein, Crystal *et al.* provide a working example of the transfection of mammalian cells in rat adipose tissue (see figures 1-4). Combined, O'Reilly *et al.* and Crystal *et al.* teach that the nucleic acid sequences encoding endostatin can be used in gene therapy protocols, and provides the specific methodology for the

delivery of endostatin through the use of adenoviral vectors. Similar to both O'Reilly *et al.* and Crystal *et al.*, Folkman *et al.* teach that administration of anti-angiogenic proteins, also termed angiostatin proteins or endothelial proliferation inhibitor proteins, are effective in preventing angiogenesis and useful in methods of treating and inhibiting angiogenesis of tumors (see abstract and examples provided on pages 2-5). Further, Folkman *et al.* teach that the anti-angiogenic proteins can be delivered by a variety of means and methods, including the use of adenoviral vectors in gene therapy protocols (pages 23-24 and 26). Each O'Reilly *et al.*, Crystal *et al.* and Folkman *et al.* teach that human endothelial cells present in a blood vessel are affected by the anti-angiogenic protein and providing an anti-angiogenic protein to cells prevent angiogenesis (for example O'Reilly *et al.* figures 8 and 12 and column 2 lines 31-42 and Folkman *et al.* pages 4-5 and 35). Each O'Reilly *et al.*, Crystal *et al.* and Folkman *et al.* use different endostatin proteins known in the art, and Blezinger *et al.* provide further evidence that various specific forms of endostatin were known and used in the art. More specifically, Blezinger *et al.* teach that administration of the polynucleotide encoding the Ig-Kappa-endostatin fusion protein results in the production of a functional endostatin protein in the serum (results summarized in figure 2). Each O'Reilly *et al.*, Crystal *et al.* and Folkman *et al.* provide expression of the anti-angiogenic proteins by expression vectors which use promoters other than the endogenous anti-angiogenic promoter, in particular Crystal *et al.* reduces to practice the use of adenoviral vectors for delivery and expression of endostatins. Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to

use the adenoviral delivery methods for the delivery of anti-angiogenic factors disclosed by Folkman *et al.* and reduced to practice by Crystal *et al.* for the delivery of the specific anti-angiogenic protein endostatin disclosed by O'Reilly *et al.* One having ordinary skill in the art would have been motivated to use an adenoviral vector for the delivery of the anti-angiogenic protein endostatin because of the specific teaching that adenoviral vectors 'are capable of transducing novel genetic sequences into target cells *in vivo*', 'have high efficiencies of infectivity' and provide high long term levels of expression of the gene of interest (Folkman *et al.* page 24, lines 5-15 and generally supported by the examples of Crystal *et al.*). There would have been a reasonable expectation of success to substitute the endostatin sequence taught by O'Reilly *et al.* for the anti-angiogenic sequences taught by Folkman *et al.* because the methods required are conventional techniques routinely used to generate vectors. Further, given the working examples of O'Reilly *et al.* and Crystal *et al.* demonstrating that endostatin can be expressed as functional molecule in various expression systems and the success of Folkman *et al.* for the expression of other anti-angiogenic proteins there would have been a reasonable expectation that an adenoviral vector would be capable of producing an active endostatin when used to infect a cells.

In summary, Folkman *et al.* Crystal *et al.* and O'Reilly *et al.* teach that human endothelial cells present in a blood vessel are affected by the anti-angiogenic protein and providing an anti-angiogenic protein to cells prevent angiogenesis (O'Reilly *et al.* figures 8 and 12 and column 2 lines 31-42 and Folkman *et al.* pages 4-5 and 35). Each O'Reilly *et al.*, Crystal

et al. and Folkman *et al.* provide expression of the anti-angiogenic proteins by expression vectors which use promoters other than the endogenous anti-angiogenic promoter. More specifically, Folkman *et al.* and O'Reilly *et al.* teach that human endothelial cells present in a blood vessel are affected by the anti-angiogenic protein and providing an anti-angiogenic protein to cells prevent angiogenesis (O'Reilly *et al.* figures 8 and 12 and column 2 lines 31-42 and Folkman *et al.* pages 4-5 and 35). Together, O'Reilly *et al.*, Crystal *et al.* and Folkman *et al.* make obvious to one having ordinary skill in the art at the time the invention was made to use the adenoviral delivery methods for the delivery of any anti-angiogenic factor as disclosed by Folkman *et al.* and for the delivery of the specific anti-angiogenic protein endostatin as disclosed by O'Reilly *et al.* Again as supported by the teaching of each O'Reilly *et al.*, Crystal *et al.*, Folkman *et al.* and Blezinger *et al.* it was known at the time of filing that anti-angiogenic proteins are proteins produced and released from cells to affect the surrounding environment of the cell. Each provide teach that it was known in the art that the affect that anti-angiogenic proteins exert is extracellularly surrounding the cells from which it is secreted. It is noted that O'Reilly *et al.* specifically teaches that endostatin provides its affect extracellularly and thus, must be secreted if produced by a cell. However, neither O'Reilly *et al.* nor Folkman *et al.* teach to use the heterologous secretion signal peptide sequence of Ig-Kappa when producing a functional anti-angiogenic proteins in cells. As noted above, Blezinger *et al.* teach a fusion protein comprising endostatin and the Ig-Kappa secretion signal (page 343, middle of second column and summarized in figure 1A). Blezinger *et al.* teach that administration of the polynucleotide

encoding the Ig-Kappa-endostatin fusion protein results in the production of endostatin in the serum (results summarized in figure 2). Blezinger *et al.* teach that expression and secretion of endostatin can be used in methods to inhibit tumor growth. Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to use the polynucleotide sequences encoding the Ig-Kappa-endostatin fusion protein as taught by Blezinger *et al.* in the adenoviral delivery methods for the delivery of anti-angiogenic factors as generally disclosed by Folkman *et al.* and more specifically disclosed by O'Reilly *et al.* and Crystal *et al.* for the delivery of the specific anti-angiogenic protein endostatin. One having ordinary skill in the art would have been motivated to use the polynucleotide sequences encoding the Ig-Kappa-endostatin fusion protein as taught by Blezinger *et al.* because of the successful results which demonstrate the production of endostatin in the serum when administered to a subject. There would have been a reasonable expectation of success to use the Ig-Kappa-endostatin fusion protein sequences with those disclosed by O'Reilly *et al.* and Folkman *et al.* to construct an adenoviral vector comprising a polynucleotide sequence encoding a Ig-Kappa-endostatin fusion protein, and to use said vector to express said protein in a cell.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Applicants have argued that the combination of O'Reilly *et al.* and Folkman *et al.* does not support the use of adenoviral vectors for the delivery of endostatin with a reasonable expectation of success. Noting the inventorship of the cited references Applicants argue that the absence of any disclosure in O'Reilly *et al.* "belies the Examiners assertion that one of skill in

the art would be motivated to combine these two references' (page 9). This argument is not found persuasive because clearly Folkman *et al.* teach that the anti-angiogenic proteins can be delivered by a variety of means and methods, including the use of adenoviral vectors in gene therapy protocols (pages 23-24 and 26) providing clear motivation in the art. Why a particular specification provides guidance to particular embodiments known in the art is in the control of the inventor(s). However, beyond the fact that adenoviral vectors were known vectors used in gene delivery at the time of filing, because as noted by Applicants both O'Reilly *et al.* and Folkman *et al.* are co-inventors, clearly both were aware of the use of adenoviral vectors for the delivery of antiangiogenic factors as evidenced by their disclosure in the specification and the oath/declaration to that fact. Additionally, the specification and the reduction to practice of Crystal *et al.* of the use of adenoviral vectors for delivery and expression of anti-angiogenic compounds clearly provides evidence and motivation for this combination.

Additionally, Applicants argue that there was no expectation of success for the ability of expressing endostatin through the use of adenoviral vectors. Applicants argue that the guidance provides at best speculation that the combination would work and note that neither O'Reilly *et al.* nor Folkman *et al.* reduce to practice the combination (bridging pages 9-10). Again beyond the fact that at the time of filing it was readily known in the art (as suggested by Folkman *et al.*) that adenoviral vectors were used to deliver and express a variety of proteins of interest, Crystal *et al.* provide clear evidence that adenoviral vectors can be used to provide expression of endostatin proteins. Moreover, it is noted that a specification does not have to reduce to practice any of the

limitations set forth in the specification. Applicants argument is not found persuasive because adenoviral vectors were well known in the art at the time of filing for use in expressing a gene of interest. Further, beyond the evidence provided by Crystal *et al.*, Applicants arguments fail to specifically address why there would not be an expectation of success in light of the art as a whole and its successful use to use adenoviral vectors to express any gene of interest. Clearly, the teaching of Folkman *et al.* provides the specific motivation for the use of adenoviral vectors, and clearly sets forth the advantages of these vectors readily known in the art.

Applicants compare the expression provided by the example in Blezinger *et al.* to that disclosed in the instant specification, and argue that one would not have predicted that such levels of expression would have been produced, indicating the use of the products produce surprising and unexpected results (top of page 11). Initially, it is noted that the chimeric endostatin sequence used by Applicants (for example in figure 8) is anticipated by the sequence disclosed by Blezinger *et al.* thus any unexpected result that could be attributed to the encoded protein would consequently be inherent to the sequence of Blezinger *et al.* More consistent and more likely, the difference seen between these two example is due to the differences in vectors used for delivery and expression. In this case, clearly the specific teaching that adenoviral vectors 'are capable of transducing novel genetic sequences into target cells *in vivo*', 'have high efficiencies of infectivity' and provide high long term levels of expression of the gene of interest taught by Folkman *et al.* (page 24, lines 5-15 and generally supported by the examples of Crystal *et al.*) provide a clear expectation that the use of adenoviral vectors would provide high and

prolonged expression of any gene of interest. Importantly, any expression level is more closely associated with the promoter that is being used to express the gene of interest that the general backbone of the vector. In the case for use of an adenoviral vector, the 'high' or 'increased' expression normally associated with the use of the vectors *in vivo* is comment on total expression levels due to the ability of a recombinant adenovirus to effectively infect cells of a particular tissue, such as the liver. The *in vivo* experiments performed by Blezinger *et al.* use plasmid vectors delivered directly to the muscle which would be expected to provide different expression levels than if one were to use an adenoviral vector and other routes of delivery. In this case the differences in the specific results relied upon by Applicants would not be considered a valid comparison because of the dissimilarity between the vectors and routes of delivery in both examples. Moreover, Crystal *et al.* reduce to practice an adenoviral vector expressing an endostatin, making obvious the use and expected expression provided by the use of adenoviral vectors as taught by Folkman *et al.* Applicants argument is not found persuasive because one would expect different vectors to provide different levels of expression, and there no evidence that the expression observed by Crystal *et al.* or that expected by the disclosure of Folkman *et al.* would be different from that set forth in the example in the instant application.

Thus, for the reasons above, the claimed invention as a whole was clearly *prima facie* obvious in light of the teaching of Folkman *et al.* Crystal *et al.*, O'Reilly *et al.* and Blezinger *et al.*

Claim 33 is rejected under 35 U.S.C. 103(a) as being unpatentable over O'Reilly *et al.* (US Patent 5,854,205), Folkman *et al.* (WO 96/35774), Crystal *et al.* (US2002/0076395 A1) and Blezinger *et al.* as applied to claims 2, 3, 28, 29, 34-37, 39, 40, 41 in further view of Lemarchand *et al.*

The teaching of O'Reilly *et al.* (US Patent 5,854,205), Folkman *et al.* (WO 96/35774), Crystal *et al.* (US2002/0076395 A1) and Blezinger *et al.* are summarized above. Briefly, Folkman *et al.* and O'Reilly *et al.* teach that human endothelial cells present in a blood vessel are affected by the anti-angiogenic protein and providing an anti-angiogenic protein to cells prevent angiogenesis (O'Reilly *et al.* figures 8 and 12 and column 2 lines 31-42 and Folkman *et al.* pages 4-5 and 35). Further, each O'Reilly *et al.*, Folkman *et al.*, Crystal *et al.* and Blezinger *et al.* provide expression of the anti-angiogenic proteins by expression vectors which use promoters other than the endogenous anti-angiogenic promoter. Together, the references make obvious to one having ordinary skill in the art at the time the invention was made to use the adenoviral vector in delivery methods for the expression of anti-angiogenic factors such as those disclosed by Folkman *et al.*, Blezinger *et al.*, Crystal *et al.* and the specific anti-angiogenic protein endostatin as disclosed by O'Reilly *et al.* At the time of filing, the RSV promoter was well known and commonly used for the expression of proteins in mammalian cells however, none of the cited references specifically teach to use the RSV promoter in an adenoviral expression system. At the time of filing Lemarchand *et al.* teach to use recombinant adenoviral vectors for expression transgenes of interest under the control of the RSV promoter. Therefore, it

would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to use the RSV promoter for the expression of anti-angiogenic factors as generally disclosed by Folkman *et al.* and Crystal *et al.* and more specifically disclosed by O'Reilly *et al.* and Blezinger *et al.*, for the delivery and expression of the specific anti-angiogenic protein endostatin with an adenoviral expression vector. Again, it was well known in the art that anti-angiogenic proteins are proteins produced and released from cells to affect the surrounding environment of the cell, and O'Reilly *et al.* and Folkman *et al.* teach the affect that anti-angiogenic proteins exert is extracellularly surrounding the cells from which it is secreted, thus one having ordinary skill in the art would have been motivated to use adenoviral vector system with the RSV promoter as taught by Lemarchand *et al.* because said system was shown to successfully infect cells of the vasculature and that it could be used to express transgenes and produce proteins in said cells. There would have been a reasonable expectation of success to use the adenoviral RSV expression system disclosed by Lemarchand *et al.* and generally supported by the vectors disclosed in Crystal *et al.* for the expression of the endostatin sequence disclosed by O'Reilly *et al.*, Folkman *et al.* and Blezinger *et al.* to provide an adenoviral vector comprising an RSV promoter operable linked to a polynucleotide sequence encoding endostatin protein and to use said vector to express said protein in a cell.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Claims 28-30, 33, 38, 45-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Reilly *et al.* (US Patent 5,854,205), Folkman *et al.* (WO 96/35774), Crystal *et al.* (US2002/0076395 A1) and Blezinger *et al.* as applied to claims 2, 3, 28, 29, 34-37, 39, 40, 41 in further view of Kovesdi *et al.*

The teaching of O'Reilly *et al.* (US Patent 5,854,205), Folkman *et al.* (WO 96/35774), Crystal *et al.* (US2002/0076395 A1) and Blezinger *et al.* are summarized above. Briefly, Folkman *et al.* and O'Reilly *et al.* teach that human endothelial cells present in a blood vessel are affected by the anti-angiogenic protein and providing an anti-angiogenic protein to cells prevent angiogenesis (O'Reilly *et al.* figures 8 and 12 and column 2 lines 31-42 and Folkman *et al.* pages 4-5 and 35). Further, each O'Reilly *et al.*, Folkman *et al.*, Crystal *et al.* and Blezinger *et al.* provide expression of the anti-angiogenic proteins by expression vectors which use promoters other than the endogenous anti-angiogenic promoter. Together, the references make obvious to one having ordinary skill in the art at the time the invention was made to use the adenoviral vector in delivery methods for the expression of anti-angiogenic factors such as those disclosed by Folkman *et al.*, Blezinger *et al.*, Crystal *et al.* and the specific anti-angiogenic protein endostatin as disclosed by O'Reilly *et al.* At the time of filing, recombinant adenoviral vectors were well known and commonly used for the expression of proteins in mammalian cells however, neither O'Reilly *et al.* nor Folkman *et al.* specifically teach to use the RSV promoter or an adenoviral promoter to express a transgene or other alterations to the adenoviral vector in the E1-E4 regions. At the time of filing Kovesdi *et al.* teach to use recombinant adenoviral vectors

for expression transgenes under the control of the RSV promoter (figure 3) and adenoviral promoters such as the E4 promoter (figure 14), and alterations to the E1-E4 regions to make replication deficient adenoviral vectors. Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to use the recombinant adenoviral vectors taught by Kovesdi *et al.* for the expression of anti-angiogenic factors as disclosed by O'Reilly *et al.*, Folkman *et al.*, Crystal *et al.* and Blezinger *et al.* for the delivery and expression of the specific anti-angiogenic protein endostatin with an adenoviral expression vector. Moreover, Kovesdi *et al.* specifically uses the A549 cell line as a complementing cell line for propagation of said recombinant adenoviral vectors (see Example 8). At the time of the claimed invention recombinant adenoviral vectors were well known and used to express transgenes in cells, and one having ordinary skill in the art would have been motivated to use adenoviral vectors disclosed by Kovesdi *et al.* with the RSV promoter and adenoviral promoters to express heterologous transgenes because with the deletions the vectors could accommodate larger transgenes (column 7, lines 30-35) and because the resulting vectors are replication defective (column 8, lines 12-44). Recombinant adenoviral vectors were well known and easily manipulated at the time of the claimed invention, and there would have been a reasonable expectation of success to use the recombinant adenoviral vectors disclosed by Kovesdi *et al.* for the expression of the endostatin sequence as disclosed by O'Reilly *et al.*, Folkman *et al.*, Crystal *et al.* and Blezinger *et al.* to provide an adenoviral vector comprising an RSV promoter or

adenoviral promoter operable linked to a polynucleotide sequence encoding endostatin protein and to use said vector to express said protein in a cell.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Claims 28, 29, 31 rejected under 35 U.S.C. 103(a) as being unpatentable over O'Reilly *et al.* (US Patent 5,854,205), Folkman *et al.* (WO 96/35774), Crystal *et al.* (US2002/0076395 A1) and Blezinger *et al.* in further view of Kovesdi *et al.* as applied to claims 2, 3, 28-30, 34-41 and 45-49 in further view of Henderson *et al.* (US Patent 6,495,130 B1).

The teaching of O'Reilly *et al.* (US Patent 5,854,205), Folkman *et al.* (WO 96/35774), Crystal *et al.* (US2002/0076395 A1) and Blezinger *et al.* are summarized above. Briefly, Folkman *et al.* and O'Reilly *et al.* teach that human endothelial cells present in a blood vessel are affected by the anti-angiogenic protein and providing an anti-angiogenic protein to cells prevent angiogenesis (O'Reilly *et al.* figures 8 and 12 and column 2 lines 31-42 and Folkman *et al.* pages 4-5 and 35). Further, each O'Reilly *et al.*, Folkman *et al.*, Crystal *et al.* and Blezinger *et al.* provide expression of the anti-angiogenic proteins by expression vectors which use promoters other than the endogenous anti-angiogenic promoter. Together, the references make obvious to one having ordinary skill in the art at the time the invention was made to use the adenoviral vector in delivery methods for the expression of anti-angiogenic factors such as those disclosed by Folkman *et al.*, Blezinger *et al.*, Crystal *et al.* and the specific anti-angiogenic protein endostatin as disclosed by O'Reilly *et al.* Kovesdi *et al.* teach specific adenoviral

vectors wherein the transgene is under the control of the RSV promoter (figure 3) and adenoviral promoters such as the E4 promoter (figure 14), and alterations to the E1-E4 regions to make replication deficient adenoviral vectors. The additional teachings of Kovesdi *et al.* make obvious the use of said adenoviral vectors for the expression of anti-angiogenic factors as generally disclosed by Folkman *et al.* and more specifically disclosed by O'Reilly *et al.* for the delivery and expression of the specific anti-angiogenic protein endostatin with an adenoviral expression vector. However, none of above references specifically teach to use the Hep3B cell line with the adenoviral vector. At the time of filing, recombinant adenoviral vectors were well known and commonly used for the expression of proteins in mammalian cells and Henderson *et al.* teach to use recombinant adenoviral vectors in Hep3B cells (column 45, starting at line 52). More specifically, Henderson *et al.* teach that recombinant adenoviral vectors deficient in E3 are cytotoxic to Hep3B cells and tumors generated by Hep3B cells. O'Reilly *et al.*, Crystal *et al.* and Folkman *et al.* teach to use adenoviral vectors expressing endostatin in methods to decrease the vascularization of tumors for potential methods of treatment of cancer in a subject. Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the recombinant adenoviral vectors taught by O'Reilly *et al.* and Folkman *et al.* with those taught by Henderson *et al.* to provide and test a more effective method for treating tumors obtained from Hep3B cells. At the time of the claimed invention recombinant adenoviral vectors were well known and used to express heterologous transgenes in a variety of cell types, and one having ordinary skill in the art would have been motivated to use adenoviral

vectors comprising a polynucleotide sequence encoding endostatin protein made obvious by O'Reilly *et al.* and Folkman *et al.* to provide an adenoviral vector and to use said vector to express said protein in Hep3B cells as taught by Henderson *et al.* in order to provide a more effective treatment and/or testing of tumors in model systems. Recombinant adenoviral vectors and their ability to infect a wide variety of cell types was well known at the time of the claimed invention. Therefore, there would have been a reasonable expectation of success to use the recombinant adenoviral vectors that express endostatin made obvious by O'Reilly *et al.* and Folkman *et al.* to infect Hep3B cells in light of the ability of Henderson *et al.* to infect HepB3 cells with similar recombinant adenoviral vectors which do not express a transgene.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Conclusion

No claim is allowed. Claims 42-44 are free of the art of record because the art fails to teach or provide adequate motivation to use the BM40 leader sequence in combination with endostatin. Claims 42-44 are objected because the depend on rejected claims.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (703) 308-2141.

Joseph T. Woitach

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